



Water as an efficient medium for the synthesis of functionalized enol ethers

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ABSTRACT

Herein we report an efficient method for synthesis of β -alkylated and β,β -dialkylated α -iodo enol ethers in water. Radical addition in aqueous medium of ethyl iodoacetate, iodoacetonitrile, and iodoacetamide to ynol ethers leads to α -iodo enol ethers with moderate to excellent yields and high stereoselectivities.

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1. Introduction

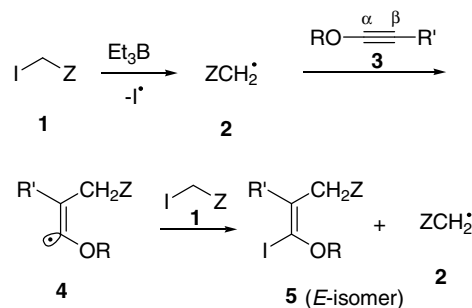
Alkyl enol ethers are ubiquitous species in organic chemistry. They have attracted the attention of many chemists, and this has led to a plethora of methods to prepare them.¹ However, methods for preparing highly substituted enol ethers² and functionalized enol ethers^{3,4} are more scarce.

We thus decided to develop a new method for preparing highly substituted and functionalized enol ethers. In addition, we wanted the method to respect as much as possible the concept of 'green chemistry'. Consequently, our first criteria was to use radical chemistry. Radical reactions can be 100% atom-economic and usually do not require environmental unfriendly reagents such as heavy metals. Secondly, we needed a green solvent known to be an efficient reaction medium for radical chemistry. Water seemed to be the obvious choice.⁵

We recently demonstrated that electron-poor radicals add to ynol ethers in organic solvent yielding enol ethers.⁴ We thus decided to explore the reaction between ethyl iodoacetate (a source of $\cdot\text{CH}_2\text{CO}_2\text{Et}$) and ynol ethers in water (Scheme 1). The electrophilic radical **2** formed by homolytic cleavage of activated methylenes **1** ($Z = \text{EWG}$, electron withdrawing group) would add to the electron-rich β -carbon of ynol ether **3** leading to vinyl radical **4**. The anti attack leading to trans-radical **4** should be favored for stereoelectronic reasons.⁶ The use of iodides, which are efficient halogen-atom transfer agents, should ensure rapid trapping of vinyl radical **4** before its interconversion. This should lead to *E*-isomer **5** with high stereoselectivity.⁷ We elected Et_3B in methanol as radical initiator because of its high miscibility with water.^{5c}

2. Radical addition of ethyl iodoacetate to ynol ethers in water

We chose different ynol ethers as starting material. The only commercially available ynol ether we could find was ethoxy-



Scheme 1.

acetylene (**3a**, $R = \text{Et}$, $R' = \text{H}$). In addition, we prepared, according to Greene's protocol,⁸ menthoxyethyne (**3b**, $R = \text{menthyl}$, $R' = \text{H}$) and menthoxypropyne (**3c**, $R = \text{menthyl}$, $R' = \text{CH}_3$). We also prepared **3d** ($R = \text{Et}$, $R' = \text{SiMe}_2\text{tBu}$), **3e** ($R = \text{Et}$, $R' = \text{SiPh}_2\text{tBu}$), and **3f** ($R = \text{adamantyl}$, $R' = \text{H}$) using standard protocols.^{4,9}

Surprisingly, we could find no examples of the use of ynol ethers in water. We thus began by testing the stability of these species in aqueous radical reaction conditions. We observed that ynol ethers **3a–f** were all stable in water, in the presence of Et_3B , for at least 24 h.

Our first test was to react commercially available ynol ether **3a** (0.10 mmol/mL of water) with ethyl iodoacetate (added in one amount) (Table 1). Since the reaction is performed in water, the reaction could not be followed by TLC. Reactions were stopped after 1–3 h, worked-up, concentrated under vacuum then analyzed. Our first result appears on entry 1. Though the major compound in the reaction mixture was the starting material (along with very little hydrolysis products), we observed a 30% yield of the desired adduct **5aa**. Though the yield was poor, we were happy to observe that the desired compound was produced with perfect regioselectivity (>99:1) and very high stereoselectivity (95:5 *E/Z*). We noted, in the reaction mixture, the presence of $(\text{CH}_2\text{CO}_2\text{Et})_2$ resulting from homocoupling of $\cdot\text{CH}_2\text{CO}_2\text{Et}$ radicals. This suggested

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Table 1
Radical addition of ethyl iodoacetate (**1a**, Z = CO₂Et) to ynol ethers ROC=CR' **3a–f**^{a,b}

Entry	Ynol ethers 3 ^c (ROC=CR')	Reaction time (h)	Temperature (°C)	Ratio α : β	Ratio E:Z ^d	Product ^{e,f}	Yield ^g (%)
1	3a (R = Et, R' = H)	1	25	>99:1	95:5	5aa (R = Et, R' = H, Z = CO ₂ Et)	30
2	3a	1	25	>99:1	95:5	5aa	60
3	3a	2	25	>99:1	92:8	5aa	71
4	3a	3	25	>99:1	90:10	5aa	80
5	3a	5	25	>99:1	90:10	5aa	65
6	3a	3	0	>99:1	92:8	5aa	85
7	3a	5	0	>99:1	92:8	5aa	87
8	3b (R = menthyl, R' = H)	3	25	>99:1	93:7	5ba (R = menthyl, R' = H, Z = CO ₂ Et)	79
9	3b	3	0	>99:1	90:10	5ba	79
10	3c (R = menthyl, R' = Me)	2	25	>99:1	92:8	5ca (R = menthyl, R' = Me, Z = CO ₂ Et)	81
11	3c	3	0	>99:1	90:10	5ca	82
12	3d (R = Et, R' = SiMe ₂ tBu)	3	25	—	—	5da (R = Et, R' = SiMe ₂ tBu, Z = CO ₂ Et)	0
13	3d	5	0	—	—	5da	0
14	3e (R = Et, R' = SiPh ₂ tBu)	3	25	—	—	5ea (R = Et, R' = SiPh ₂ tBu, Z = CO ₂ Et)	0
15	3e	5	0	—	—	5ea	0
16	3f (R = adamantyl, R' = H)	5	25	—	—	5fa (R = adamantyl, R' = H, Z = CO ₂ Et)	0

^a The radical initiator, Et₃B 1.0 M/MeOH, was added every 15 min (100 μ L).

^b 3 equiv of ethyl iodoacetate was added. 0.5 equiv was added every 30 min except for entry 1 where 3 equiv was added at the beginning of the reaction.

^c Dispersion of ynol ethers **3** in water: 0.10 mmol/mL.

^d Determined by GC.

^e Compounds **5aa**, **5ba**, and **5ca** previously reported in the literature were characterized by comparing their ¹H NMR, IR, and MS spectra to the published data (see Ref. 4).

^f The isomers resulting from addition at the α position were never detected by ¹H NMR, GCMS, and TLC.

^g Yields obtained by ¹H NMR (internal standard: diphenylmethane).

that a too high concentration of the radical precursor was used. Also, we noted that ynol ether **3a** was unstable when a high quantity of ethyl iodoacetate (higher than 0.95 equiv) was present. In order to maintain a lower concentration of the radical precursor (ethyl iodoacetate) in the reaction medium, we thus decided to add the radical source by small amounts of 0.5 equiv every 30 min. As can be seen from entry 2, this allowed to double the efficiency of the yield (from 30% in entry 1 to 60% in entry 2). Note that addition of more than 3 equiv of ethyl iodoacetate did not lead to better yields (not present in the Table). The reaction at 25 °C gave even better results after 3 h (entry 4, 80% yield). Longer period of time (entry 5, 5 h) resulted in partial decomposition of the desired compound, lowering the yield to 65%. The reaction was most efficient at 0 °C (87% yield after 5 h (entry 7)). We think that this higher yield is most probably due to a decrease of the decomposition rate of the desired adduct **5aa** at 0 °C. In all cases, stereoselectivities were always higher than 9–1 in favor of the E isomer. Note that for the same reaction in CH₂Cl₂,⁴ observed yields were slightly better (97%, see Ref. 4).

We then turned to a much more sterically demanding ynol ether, compound **3b**. We were quite intrigued to see how this very 'organic' compound (compared to **3a**) would behave in water. Again, the reaction proceeded smoothly in water with very interesting yields (79% at 0 °C and at 25 °C, entries 8 and 9). With the even more sterically demanding **3c**, the reaction occurred with

comparable yields (81–82%, entries 10 and 11). Note that in that case, a tetrasubstituted enol ether (**5ca**) was formed. We next turned to even more sterically demanding ynol ethers. Ynol ethers with secondary alkyl groups (**3**, R' = *i*Pr, *s*Bu)⁸ were very difficult to work with. Their high instability in water precluded the possibility of any radical reaction. However, ynol ethers **3d** (R = Et, R' = *Si*tBuMe₂) and **3e** (R = Et, R' = *Si*tBuPh₂) were quite stable in water. The results of addition of ethyl iodoacetate to **3d** and **3e** are reported in entries 12–15. As one can see, we could not make the reaction work with these very encumbered acetylenic ethers. Only the starting material was recovered (along with little decomposition). Reactivity of ynol ether **3f** (R = adamantyl, R' = H) was also assessed. Unfortunately, in that case also, we could not observe any desired adduct (entry 16). Note that for all the very sterically demanding ynol ethers (**3d–f**), we tried to push the reaction further by letting it run for 24–48 h. This did not give better results (0% yield). After this long period of time, hydrolysis of ynol ethers was observed.

3. Radical addition of iodoacetonitrile and iodoacetamide to ynol ether **3c** in water

We then changed ethyl iodoacetate for another source of electron-poor radical. We tried to react iodoacetonitrile with ynol ether **3c**. The results are gathered in Table 2. The reaction also

Table 2
Radical addition of iodoacetonitrile (**1b**, Z = CN) to ynol ethers **3c**^a

Entry	Ynol ether 3 ^b (ROC=CR')	Reaction time (h)	ICH ₂ CN ^c (equiv)	Temperature (°C)	Ratio α : β	Ratio E:Z ^d	Product ^{e,f}	Yield ^g (%)
1	3c (R = menthyl, R' = Me)	2, 5	3	25	>99:1	96:4	5cb (R = menthyl, R' = Me, Z = CN)	24
2	3c	4	4	25	>99:1	97:3	5cb	44
3	3c	5	5	25	>99:1	95:5	5cb	59
4	3c	5	5	0	>99:1	92:8	5cb	58
5	3c	1	5	100	—	—	5cb	0

^a The radical initiator, Et₃B 1.0 M/MeOH, was added every 15 min (100 μ L).

^b Dispersion of ynol ethers **3c** in water: 0.10 mmol/mL.

^c 0.5 equiv was added every 30 min until the predetermined quantity was reached.

^d Determined by GC.

^e Compound **5cb** previously reported in the literature was characterized by comparing ¹H NMR and IR spectra to the published data (see Ref. 4).

^f The compound resulting from addition at the α position was never detected by ¹H NMR, GCMS, and TLC.

^g Yields obtained by ¹H NMR (internal standard: diphenylmethane).

Table 3
Radical addition of iodoacetamide (**1c**, Z = CONH₂) to ynol ethers **3c**^a

Entry	Ynol ether 3c ^b (ROC=CR')	Reaction time (h)	ICH ₂ CONH ₂ ^c (equiv)	Temperature (°C)	Ratio α:β	Ratio E:Z ^d	Product ^e	Yield ^f (%)
1	3c (R = menthyl, R' = Me)	4.5	3	25	>99:1	>99:1	5cc (R = menthyl, R' = Me, Z = CONH ₂)	38
2	3c	24	5	25	—	—	5cc	0
3	3c	0.5	1	80	—	—	5cc	0
4	3c	1	5	100	—	—	5cc	0

^a The radical initiator, Et₃B 1.0 M/MeOH, was added every 15 min (100 μL) except for entry 2 where Et₃B was added every 60 min for the first 6 h only.

^b Dispersion of ynol ethers **3c** in water: 0.10 mmol/mL.

^c 1.0 equiv was added every 90 min until the predetermined quantity was reached.

^d Determined by GC.

^e Compound **5cc** previously reported in the literature was characterized by comparing ¹H NMR and IR spectra to the published data (see Ref. 4).

^f Yields obtained by ¹H NMR (internal standard: diphenylmethane).

occurred with this new source of radical (entry 1, 24% yield). The yield of the desired adduct was improved by adding higher amount of the radical source (entries 2 and 3, up to 59% yield). However, we could not obtain yields as good as those observed with ethyl iodoacetate (up to 82% yield with **3c**). Reaction at 0 °C did not give better results (entry 4, 58% yield). In order to improve these low yields using iodoacetonitrile, we raised the temperature to 100 °C for 1 h (entry 5). Unfortunately, we observed no desired adduct. Only decomposition of ynol ether **3c** was observed.

Iodoacetamide was also reacted with ynol ether **3c** under these radical reaction conditions. Table 3 shows that the reaction worked (entry 1), but with a modest yield. Increasing the reaction time to 24 h (entry 2) or elevating the temperature to 80 °C (entry 3) or to 100 °C (entry 4) only led to decomposition.

4. Radical addition of ethyl bromoacetate and methyl halides to ynol ethers in water

Finally, we examined the possibility of using BrCH₂CO₂Et as radical precursor instead of ICH₂CO₂Et. We knew, however, that the process might be slow since it is known that the bromine atom is a poorer atom transfer agent than iodine. Nevertheless, we tried to react ethyl bromoacetate with ynol ether **3a** and **3c**. Even after 24 h, no desired adduct could be observed. We also envisaged the possibility of using CH₃Br and CH₃I as radical precursors. We expected, however, CH₃ radicals to add less efficiently to electron-rich ynol ethers since they are less electrophilic than ·CH₂Z (Z = EWG) radicals. Again, after 24 h, neither methyl bromide, nor methyl iodide could lead to any desired adduct.

In conclusion, we have shown that electron-poor carbon-centered radicals add to ynol ethers in water with modest to high yields. The enol ethers produced are highly substituted and functionalized. The method even allows the production of completely substituted enol ether (production of **5c**). The best yields (up to 87% at 0 °C) were obtained when ethyl iodoacetate was used as radical precursor. Iodoacetonitrile reacts modestly while iodoacetamide adds poorly. The reaction does not occur with very bulky triple bonds. Ethyl bromoacetate, methyl bromide, and methyl iodide do not add to ynol ethers in water. To the best of our knowledge, it is the first method allowing the production of enol ethers in water.

5. Typical procedure for the radical addition of ethyl iodoacetate to ynol ether in water

In a 10 mL round-bottomed flask, 0.90 mmol of ynol ether and 0.5 equiv of XCH₂Z were dissolved in 9.0 mL of freshly distilled water at the desired temperature. Triethylborane (1.0 M in methanol) was added (100 μL) to initiate the radical chain process. Triethylborane (100 μL) was then added every 15 min until the end of reaction (except for 24 h reactions where Et₃B was added every

60 min for the first 6 h only). XCH₂Z was added every 30 min (0.5 equiv) until the predetermined quantity was reached. Once the predetermined reaction time was reached, sodium chloride was added to the reaction mixture, followed by three hexane extractions. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The solvent was removed by a gentle flow of dry nitrogen gas.

6. Typical procedure for the NMR yield using an internal standard

In an NMR tube, a precisely weighed quantity of the crude addition reaction mixture and a known quantity of diphenylmethane (internal standard) were dissolved in CDCl₃ or in C₆D₆. The yield was obtained by comparing the integration of the CH₂ signal of diphenylmethane (3.9 ppm) with the integration of the allylic CH₂ signal of the desired product (3.2–3.4 ppm).

7. Preparation of the 1.0 M Et₃B solution in methanol

In a thoroughly washed, dried, and nitrogen purged flask, 17.1 mL of freshly distilled and nitrogen purged methanol was added, followed by 2.9 mL of nitrogen purged pure triethylborane. **WARNING!** Purging with nitrogen was essential in order to avoid any spontaneous fire. The methanolic solution of triethylborane must be kept in the refrigerator. It was stable for approximately 2 weeks. Note that once dissolved in methanol, triethylborane was no longer pyrophoric.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.165.

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